

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau

10/529850

(43) International Publication Date  
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number  
WO 2004/032975 A3(51) International Patent Classification<sup>7</sup>: A61K 51/04(21) International Application Number:  
PCT/US2003/031466

(22) International Filing Date: 6 October 2003 (06.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/415,824 4 October 2002 (04.10.2002) US

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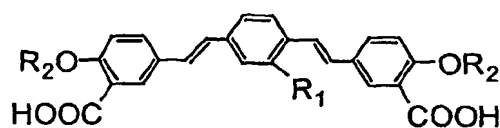
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations

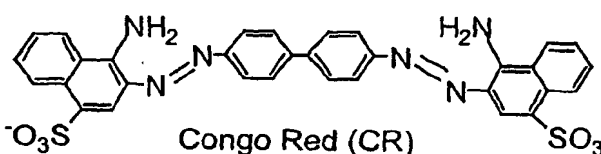
[Continued on next page]

(54) Title: BIPHENYLS AND FLUORENES AS IMAGING AGENTS IN ALZHEIMER'S DISEASE

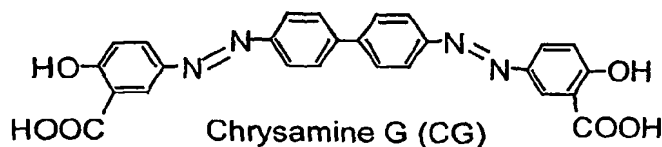


Styrylbenzene (SB)

	R <sub>1</sub>	R <sub>2</sub>
X-34	H	H
BSB	Br	H
ISB	I	H
IMSB	I	Me



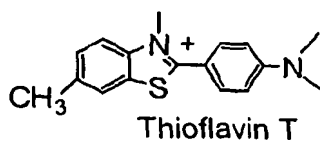
Congo Red (CR)



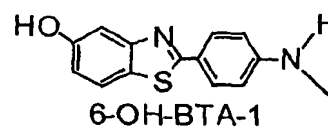
Chrysamine G (CG)



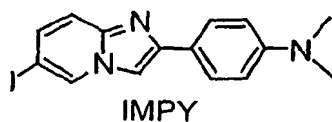
FDDNP



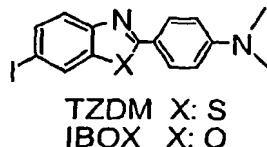
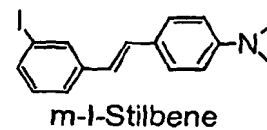
Thioflavin T



6-OH-BTA-1



IMPY

TZDM X: S  
IBOX X: O

m-I-Stilbene

(57) Abstract: This invention relates to a method of imaging amyloid deposits and to labeled compounds, and methods of making labeled compounds useful in imaging amyloid deposits. This invention also relates to compounds, and methods of making compounds for inhibiting the aggregation of amyloid proteins to form amyloid deposits, and a method of delivering a therapeutic agent to amyloid deposits.



- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

**(88) Date of publication of the international search report:**  
16 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT 03/31466

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K51/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, COMPENDEX, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	LEE C-W ET AL: "Dimethylamino-fluorenes: ligands for detecting beta-amyloid plaques in the brain" NUCLEAR MEDICINE AND BIOLOGY, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 30, no. 6, August 2003 (2003-08), pages 573-580, XP004444175 ISSN: 0969-8051 the whole document	1-9, 34-36
X	----- DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; REISSERT, ARNOLD: "Attempts to prepare substituted indigos" XP002270065 retrieved from STN Database accession no. 8:10644 abstract	1-9, 34-36

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

12 February 2004

Date of mailing of the International search report

02.07.2004

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Authorized officer

Winger, R

## INTERNATIONAL SEARCH REPORT

 Inte Application No  
 PCT 03/31466

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& BER. , 47, 672-81, 1914, ----- DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VORLANDER, D.: "The doctrine of intramolecular oppositions and the directing of substituents in benzene. II" XP002270066 retrieved from STN Database accession no. 20:4855 abstract & BER. , 58B, 1893-914, 1925, -----	1-9, 34-36
X	US 2 157 071 A (MOORE GARNETT V ET AL) 2 May 1939 (1939-05-02) examples -----	1-9, 34-36
X	DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; THEILACKER, WALTER ET AL: "Dye theory. Triarylmethane dyes of the biphenyl series. II" XP002270004 retrieved from STN Database accession no. 51:17167 abstract & CHEMISCHE BERICHTE , 89, 970-83 CODEN: CHBEAM; ISSN: 0009-2940, 1956, -----	1-9, 34-36
X	DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BARKER, C. C. ET AL: "Steric effects in di- and triarylmethanes. VII. Biphenyl analogs of crystal violet and malachite green" XP002270067 retrieved from STN Database accession no. 56:18064 abstract & JOURNAL OF THE CHEMICAL SOCIETY, ABSTRACTS 3445-8 CODEN: JCSAAZ; ISSN: 0590-9791, 1961, -----	1-9, 34-36
X	US 3 821 293 A (ADAMS S ET AL) 28 June 1974 (1974-06-28) claim 1 -----	1-9, 34-36
X	AU 545 825 B (FMC CORP) 1 August 1985 (1985-08-01) claims -----	1-9, 34-36
	-/--	

## INTERNATIONAL SEARCH REPORT

 Int'l Application No  
 PCT/93/31466

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/24115 A (UNIV BRITISH COLUMBIA) 9 December 1993 (1993-12-09) page 1, paragraph 1; claim 4 -----	1-9, 34-36
X	US 5 739 166 A (REITZ DAVID B ET AL) 14 April 1998 (1998-04-14) claims 1,27; examples 1,8-10,12 -----	1-9, 34-36
X	WO 99/41224 A (BAYLY CHRISTOPHER I ; MERCK FROSST CANADA INC (CA); BLACK CAMERON (CA)) 19 August 1999 (1999-08-19) claims 5,15; example 3 -----	1-9, 34-36
Y	WO 98/47969 A (MATHIS CHESTER A JR ; KLUNK WILLIAM E (US); PETTEGREW JAY W (US); UNIV) 29 October 1998 (1998-10-29) page 51, paragraph 3; claims 1,2 -----	1-9, 34-36
Y	KLUNK W E ET AL: "DEVELOPMENT OF SMALL MOLECULE PROBES FOR THE BETA-AMYLOID PROTEIN OF ALZHEIMER'S DISEASE" NEUROBIOLOGY OF AGING, TARRYTOWN, NY, US, vol. 15, no. 6, 1994, pages 691-698, XP000602786 ISSN: 0197-4580 figure 1 -----	1-9, 34-36

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 03/31466

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-9, 34-36 (partly)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the compounds mentioned in the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 34-36 (partly)

A compound of general formula I, compositions and uses thereof.

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2. claims: 10-15, 34-36 (partly)

A compound of general formula II, compositions and uses thereof.

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3. claims: 16-28, 34-36 (partly)

A compound of general formula III and a radioisotope complex, compositions and uses thereof.

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4. claims: 29-30, 34-36 (partly)

A compound of general formula IV and a radioisotope complex, compositions and uses thereof.

---

5. claims: 31, 34-36 (partly)

A compound of general formula V, compositions and uses thereof.

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6. claims: 32-33, 34-36 (partly)

A compound of general formula VI and a radioisotope complex, compositions and uses thereof.

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# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/US2003/31466

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2157071	A	02-05-1939	NONE	
US 3821293	A	28-06-1974	GB 1091403 A	15-11-1967
			BE 658723 A	22-07-1965
			CH 454822 A	30-04-1968
			CH 501577 A	15-01-1971
			CS 163157 B2	29-08-1975
			CS 163156 B2	29-08-1975
			DE 1518528 A1	27-02-1969
			DK 127251 B	08-10-1973
			DK 116794 B	16-02-1970
			FI 42712 B	30-06-1970
			FR 5737 M	04-03-1968
			FR 1430359 A	04-03-1966
			FR 5738 M	29-01-1968
			IL 22772 A	27-02-1969
			NL 6500865 A ,B	26-07-1965
			SE 324759 B	15-06-1970
			SE 329843 B	26-10-1970
			US 3755427 A	28-08-1973
			US 3784705 A	08-01-1974
			US 3793457 A	19-02-1974
			US 4053639 A	11-10-1977
AU 545825	B	01-08-1985	AU 545825 B2	01-08-1985
			AU 8881682 A	03-03-1983
WO 9324115	A	09-12-1993	US 5192753 A	09-03-1993
			WO 9324115 A1	09-12-1993
			DE 69224080 D1	19-02-1998
			DE 69224080 T2	30-07-1998
			EP 0642336 A1	15-03-1995
			JP 7506559 T	20-07-1995
US 5739166	A	14-04-1998	AT 193525 T	15-06-2000
			AU 4284196 A	19-06-1996
			CA 2206257 A1	06-06-1996
			DE 69517333 D1	06-07-2000
			DE 69517333 T2	30-11-2000
			DK 794942 T3	14-08-2000
			EP 0794942 A1	17-09-1997
			ES 2146791 T3	16-08-2000
			GR 3033828 T3	31-10-2000
			JP 10509975 T	29-09-1998
			PT 794942 T	30-11-2000
			WO 9616934 A1	06-06-1996
WO 9941224	A	19-08-1999	AT 253545 T	15-11-2003
			AU 749618 B2	27-06-2002
			AU 2506599 A	30-08-1999
			CA 2318966 A1	19-08-1999
			WO 9941224 A1	19-08-1999
			DE 69912581 D1	11-12-2003
			EP 1054857 A1	29-11-2000
			JP 2002503647 T	05-02-2002
			US 5994379 A	30-11-1999
WO 9847969	A	29-10-1998	US 6168776 B1	02-01-2001

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/03/31466

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9847969	A	AU 7136998 A	13-11-1998
		BR 9809580 A	19-06-2001
		CA 2286607 A1	29-10-1998
		CN 1261906 T	02-08-2000
		EE 9900503 A	15-06-2000
		EP 0977815 A1	09-02-2000
		HU 0003804 A2	28-06-2001
		JP 2002500634 T	08-01-2002
		NO 995088 A	17-12-1999
		NZ 500714 A	28-09-2001
		PL 336321 A1	19-06-2000
		SK 144099 A3	11-07-2000
		TR 9903115 T2	22-05-2000
		WO 9847969 A1	29-10-1998
		US 6133259 A	17-10-2000
		US 6114175 A	05-09-2000
		ZA 9803301 A	20-10-1999